Strategies to Enhance Detection and Treatment of Unrecognized Chronic Kidney Disease

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Many patients seen in primary care have chronic kidney disease (CKD), an increasingly prevalent, costly, and underappreciated public health problem. According to the third National Health and Nutrition Examination Survey (NHANES III), 800,000 Americans have serum creatinine levels of 2.0 mg/dL or greater, and 6.2 million people have levels of 1.5 mg/dL or greater [1]. Although these creatinine values include those only modestly greater than the upper limit of normal and therefore suggest very mild and clinically insignificant disease, they correspond to glomerular filtration rates of less than 60 mL/min/1.73 m². This translates into approximately a 40% reduction in renal function.

CKD is a multifaceted disease process. Objectives of nephrology interventions for CKD include (1) a reduction in the incidence rates for end-stage renal disease (ESRD), (2) an increase in screening for kidney disease in persons with hypertension and diabetes mellitus, (3) an increase in the treatment to preserve kidney function in persons with diabetes and proteinuria, (4) optimization of blood pressure control in persons with kidney disease, and (5) an improvement in pre-ESRD care to decrease ESRD-related morbidity, mortality, and costs [2]. Early intervention will likely have the greatest impact on slowing progression of CKD and thus delay the development of ESRD. However, before a physician can initiate effective treatment or refer a patient to a nephrologist, a diagnosis must be made. It can be difficult to diagnose CKD in its early stages, when it is usually asymptomatic. Challenges include identifying patients at risk and applying appropriate screening, interpreting flawed measures for evaluating renal function, and contending with the lack of uniform nomenclature in the medical literature. This article will discuss these challenges and recommend strategies for overcoming them.

Identifying Patients at Risk

Traditional risk factors for CKD have been hypertension and diabetes mellitus. However, recent data have shown that age, male sex, non-Caucasian race (black, Native American, and Asian/Pacific Islander) and ethnicity (Latino) are also important predictors of kidney disease [1,3]. Blacks in particular show a disproportionate risk among both hypertensive and diabetic patients. Even after controlling for a higher prevalence of diabetes mellitus, blacks have an almost threefold increased risk for the development of ESRD [4]. Guidelines for screening, diagnosis, and optimal treatment of diabetic nephropathy and hypertension are widely available [5–7] and will be discussed here only briefly.

Identification and Treatment of Diabetic Nephropathy

Diabetic nephropathy is the most common single reported cause of ESRD in the United States, and the proportion of affected patients continues to grow [8] (Figure 1). About 20% to 30% of patients with type 1 or type 2 diabetes develop evidence of nephropathy. Incidence of diabetic ESRD is lower in patients with type 2 diabetes compared with type 1 [4], but because type 2 diabetes is more prevalent the burden of CKD from type 2 diabetes is far greater. Current guidelines advocate yearly screening with urinalysis for evidence of overt proteinuria, which is a strong risk factor for the development of progressive disease and ESRD [9–12]. If the urinalysis is negative for overt albuminuria, a test for the presence of microalbumin is necessary. Microalbuminuria is defined as the excretion of more than 30 mg of albumin per 24 hours and is the earliest manifestation of nephropathy as well as a strong predictor for the development of overt nephropathy among patients with type 1 diabetes [13] and mortality among patients with type 2 diabetes mellitus [14].

Because of the high proportion of patients who progress from microalbuminuria to overt nephropathy and ESRD, the American Diabetes Association recommends the use of angiotensin-converting enzyme (ACE) inhibitors for all hypertensive diabetics and for normotensive type 1 patients with microalbuminuria [6]. It is unclear to what extent the efficacy of these agents is a function of their blood pressure lowering effects versus their ability to modify abnormal protein trafficking, which is angiotensin II dependent [15]. Tight
glycemic control, aggressive antihypertensive treatment, and the use of ACE inhibitors (or angiotensin II–receptor blockers) will slow the rate of progression of diabetic nephropathy [16–22]. Treatment of diabetic nephropathy caused by type 2 diabetes is slightly more controversial, with studies suggesting a benefit from both ACE inhibitors and nondihydropyridine calcium channel blockers [23–25]. The role of angiotensin II–receptor blockers in the treatment of type 2 diabetic nephropathy is currently being investigated [26].

Diagnosis and Treatment of Hypertension
Hypertension is the second most common single reported cause of ESRD in the United States [8] (Figure 1) but may be overdiagnosed in blacks [27,28]. Initial laboratory studies for patients with elevated blood pressure should include serum creatinine concentration and urinalysis. For patients who have high-normal blood pressure as well as renal insufficiency, congestive heart failure, or diabetes mellitus, the sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure advocates consideration of prompt pharmacologic therapy, specifically with the use of an ACE inhibitor if not contraindicated [29]. These patients are considered to be at highest risk for cardiovascular events. Lifestyle modifications are recommended for the minimization of target organ damage; these include weight reduction and management, moderation of dietary sodium, use of the Dietary Approaches to Stop Hypertension (DASH) diet for stage 1 and 2 hypertension only (systolic blood pressure > 140 and < 180 mm Hg, diastolic blood pressure > 90 and < 110 mm Hg), moderation of alcohol intake, adequate physical activity, and avoidance of tobacco. Current guidelines advocate blood pressure control to 130/85 mm Hg or lower [29]. Among patients with proteinuria in excess of 1.0 g/24 hours, blood pressure should be reduced to 125/75 mm Hg or lower [29]. Pharmacotherapy should be tailored to the individual patient, especially when the patient has CKD. Multiple studies have shown the benefit of ACE inhibitors or angiotensin-receptor blocker therapy for patients with chronic proteinuric nephropathies [30–33]. All patients with evidence of renal impairment and/or proteinuria should be considered for ACE inhibitor therapy and evaluation by a nephrologist.

Adherence to Practice Guidelines
Despite the availability of published guidelines for the diagnosis and treatment of hypertension and diabetic nephropathy, recent audits of patient records show that adherence to guidelines is unsatisfactory [34,35]. Among age-eligible Medicare beneficiaries, only 12.5% of hypertensive and 7.8% of diabetic patients with 1+ or greater dipstick proteinuria had abnormal renal function mentioned in their discharge summaries. Similar patterns were observed among patients with serum creatinine levels of 2 mg./dL or greater. Despite evidence indicating substantial risk of renal function impairment, clinicians failed to recognize CKD among hypertensive patients, even those with diabetes [35].

Interpreting Imprecise Measures of Renal Function
Glomerular filtration rate (GFR) is a commonly used measure of kidney function. However, it is often difficult to define a “normal range” for GFR due to physiologic variability in
Serum creatinine is readily available and is often used to estimate renal function. However, this is an insensitive measure of GFR. Changes in serum creatinine levels do not correlate linearly with changes in GFR [38]. Because of the curvilinear relationships, among patients with early renal impairment a small increase in serum creatinine level may reflect a large percent decrease in renal glomerular function. This is very striking until the GFR falls below 60 mL/min/1.73 m² (Figure 2). Conversely, when the GFR falls below 30 mL/min/1.73 m², large increases in serum creatinine correlate with relatively small changes in GFR. Moreover, the range of creatinine values is physiologically restricted, and measurement error can make it difficult to reliably show small absolute differences in creatinine levels. Most patients with even mildly elevated serum creatinine levels may have lost approximately 50% of their GFR and already have mild to moderate kidney disease of substantial physiologic significance. Furthermore, serum creatinine levels are dependent upon many factors other than GFR, which include muscle mass, diet, sex, certain drugs, and age. Creatinine production decreases with age, and therefore their GFR and already have mild to moderate kidney disease of substantial physiologic significance. Furthermore, serum creatinine levels are dependent upon many factors other than GFR, which include muscle mass, diet, sex, certain drugs, and age. Creatinine production decreases with age, and therefore creatinine clearance to be estimated from the serum creatinine in a patient with stable renal function. For example, CKD in a 70-kg man aged 70 years with a creatinine of 1.3 mg/dL may go unnoticed despite that fact that his estimated GFR is only halving of the GFR. Relatively large declines in GFR from normal are associated with small increases in SCr until GFR falls to below 60 mL/min; further small decrements are associated with large increases in SCr.

Serum creatinine is the most common method used to estimate renal function, although the normal range of GFR is difficult to ascertain, it is more important to follow values longitudinally and observe for decline. Since GFR cannot be measured directly, renal clearance of markers that are freely filtered and excreted by the kidneys are used to estimate GFR. Techniques using radiolabeled contrast markers such as iothalamate are expensive and not widely available for clinical use. Subsequently, GFR is commonly estimated by using either the serum creatinine concentration or a creatinine clearance based on a 24-hour urine collection.

Creatinine is derived from the metabolism of creatine in skeletal muscle and from dietary meat intake. Creatinine is released into the circulation at a relatively constant rate and therefore has a relatively stable plasma concentration. However, the steady-state serum creatinine level is determined by multiple factors that include muscle mass, rate of metabolism of muscle protein creatine to creatinine, absorption of dietary creatine, and filtration and secretion of creatinine through the kidney and tubules, respectively. Creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized. However, approximately 15% of urinary creatinine is derived from creatinine secreted by the renal tubules [38]. Serum creatinine is the most common method used to estimate renal function.

Problems with Using Serum Creatinine to Estimate GFR
Serum creatinine is readily available and is often used to screen for CKD. However, this is an insensitive measure of GFR. Changes in serum creatinine levels do not correlate linearly with changes in GFR [38]. Because of the curvilinear relationships, among patients with early renal impairment a small increase in serum creatinine level may reflect a large percent decrease in renal glomerular function. This is very striking until the GFR falls below 60 mL/min/1.73 m² (Figure 2). Conversely, when the GFR falls below 30 mL/min/1.73 m², large increases in serum creatinine correlate with relatively small changes in GFR. Moreover, the range of creatinine values is physiologically restricted, and measurement error can make it difficult to reliably show small absolute differences in creatinine levels. Most patients with even mildly elevated serum creatinine levels may have lost approximately 50% of their GFR and already have mild to moderate kidney disease of substantial physiologic significance. Furthermore, serum creatinine levels are dependent upon many factors other than GFR, which include muscle mass, diet, sex, certain drugs, and age. Creatinine production decreases with age, and therefore a creatinine value that is within the “normal range” in an elderly patient may represent a significant decline in GFR but go unnoticed.

Problems with Using Creatinine Clearance to Estimate GFR
Creatinine clearance is the most widely used test to estimate GFR; however, this procedure also is prone to inaccuracies [38–40]. Because approximately 15% of urinary creatinine is excreted via secretion through the organic cation pathways in the proximal tubule [38], changes in this parameter can influence the serum creatinine concentration independent of the GFR. Therefore, the formula GFR = [UCr × V]/P, would overestimate the true GFR by at least the 10% to 15% of urinary creatinine that is derived from tubular secretion [38,40]. Furthermore, this secretion is augmented by remnant renal tubules as the disease worsens, thereby overestimating GFR during progressive deterioration of renal function [38]. Also, 24-hour clearance collections are often incomplete, especially among patients such as diabetics who may have autonomic dysfunction that compromises bladder emptying. In these situations, the true GFR will vary throughout the day and night. This contention is supported by the observation that the creatinine concentration varies diurnally and in relation to meals [41,42].

The Cockcroft-Gault Formula
A formula to take into account the increase in creatinine production with increasing weight and decline in creatinine production with age and female sex was devised: the Cockcroft-Gault formula [43]. This calculation allows the creatinine clearance to be estimated from the serum creatinine in a patient with stable renal function. For example, CKD in a 70-kg man aged 70 years with a creatinine of 1.3 mg/dL may go unnoticed despite that fact that his estimated GFR is only...
50 mL/min when calculated using the Cockcroft-Gault formula. Using this measure of renal function rather than the conventional reliance on serum creatinine concentration will facilitate the identification of CKD and likewise minimize the likelihood that patients with CKD will be overdosed with renally excreted medications.

The Cockcroft-Gault formula for creatinine clearance in mL/min =

\[
\frac{(140 - \text{age}) \times \text{lean body weight [kg]}}{\text{SCr [mg/dL]} \times 72}
\]

The value obtained must be multiplied by 0.85 in women, reflecting their reduced muscle mass compared with men [43].

A regression equation has been derived using patient-level information from the Modification of Diet for Renal Disease trial to more accurately estimate GFR using serum creatinine [44]. However, this equation requires the measurement of serum albumin concentration, which may limit its application. Moreover, its improvement over the Cockcroft-Gault formula is modest. However, either formula is a substantial improvement over the serum creatinine concentration for enhancing the accuracy of the diagnosis of CKD.

**Need for Uniform Nomenclature**

Adding to the difficulty in diagnosis and treatment of CKD is the absence of a uniform nomenclature to describe the varying severity of CKD in the clinical guidelines and medical literature. Multiple terms such as chronic renal insufficiency, chronic renal failure, chronic renal impairment, chronic renal disease, chronic kidney disease, and kidney insufficiency have been used to describe patients with varying decrements in GFR [45]. This makes it difficult for physicians and/or patients to access literature pertaining to a particular level of renal dysfunction. The development and implementation of a well-defined and conventional lexicon may help overcome these difficulties. Our suggested approach is to use the term chronic kidney disease, which could be stratified into mild, moderate, and severe categories using GFR criteria. For example, current guidelines for renal transplantation use a GFR cutoff of 80 mL/min/1.73 m² for potential donors [46]; therefore, a GFR of less than 80 mL/min/1.73 m² could be the upper limit of the range that would designate mild CKD. Lower ranges of GFRs could designate moderate and severe CKD, respectively. We would suggest an additional category of CKD designated by a GFR below 15 mL/min/1.73 m² or initiation of renal replacement therapy.

**Conclusion and Recommendations**

The number of Americans who have evidence of CKD and are therefore at risk for the development of ESRD continues to grow, especially among diabetic, hypertensive patients and racial minorities. Effective treatment can delay progressive failure among these high-risk groups when these interventions are appropriately administered during the early stages of CKD. In addition, multiple studies have outlined the increased morbidity, mortality, and medical costs associated with delayed referrals or suboptimal care of CKD patients prior to initiation of renal replacement therapy [47–57]. Despite readily available clinical practice guidelines, physicians have performed inadequately with regards to detection and treatment of CKD.

The Table lists our recommendations to enhance the identification and treatment of CKD. Physicians must identify and screen at-risk populations and correctly interpret imprecise measures of GFR in order to recognize early CKD. Given the limitations of diagnostic tools used to estimate GFR, one must not overlook serum creatinine levels that fall within “normal ranges,” especially when the patient belongs to a high-risk group. We recommend using the serum creatinine concentration to calculate creatinine clearance using the Cockcroft-Gault or a similar formula. The clinician is reminded that small changes in the steady-state creatinine concentration, even within the normal range for creatinine values, may result from large fluctuations in GFR. After CKD is identified, further attention and emphasis must be placed on maintaining blood pressure and glucose below benchmark values as well as using ACE inhibitors and/or angiotensin-receptor blockers. Easily identified risk factors for acute renal failure, such as urinary outflow obstruction or exposure to nephrotoxic agents (eg, nonsteroidal anti-inflammatory agents, aminoglycoside antibiotics, contrast dye) should be identified and exposure minimized among patients with underlying CKD. Patients with CKD should be referred to a nephrologist early in their course to assist in stratification of their risk for progressive kidney disease and to assist in developing strategies to decrease morbidity, mortality, and costs associated with CKD.

**References**


Table. Strategies to Enhance Detection and Treatment of Chronic Kidney Disease (CKD)

<table>
<thead>
<tr>
<th>1. Identify at-risk patients</th>
<th>Racial and ethnic minorities (black, Native American, Asian/Pacific Islander, Latino) Elderly Male sex Patients with diabetes mellitus, hypertension, or proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Apply appropriate screening</td>
<td>Blood pressure monitoring Serum creatinine Urinalysis Microalbumin, especially for patients with diabetes</td>
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<tr>
<td>3. Calculate creatinine clearance using the Cockcroft-Gault formula to identify CKD ( (GFR &lt; 80 \text{ mL/min}/1.73 \text{ m}^2) )</td>
<td>( \frac{[140 - \text{age}] \times \text{lean body weight [kg]}}{\text{SCR [mg/dL]} \times 72} ) Multiply by 0.85 for women</td>
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<tr>
<td>4. Follow currently existing clinical guidelines and initiate appropriate therapy to delay the progression of CKD</td>
<td>Appropriate glycemic and blood pressure control: ( \text{HbA}_{1c} ) of 7% ( \text{SBP} \leq 130 \text{ mm Hg}, \text{DBP} \leq 85 \text{ mm Hg} (\text{SBP} \leq 125 \text{ mm Hg}, \text{DBP} \leq 75 \text{ mm Hg for patients with renal insufficiency and proteinuria &gt; 1g/24 hr}) ) Initiation of ACE inhibitors if not contraindicated for all type 1 diabetes, type 2 diabetes with hypertension, and patients with evidence of renal impairment and/or proteinuria</td>
</tr>
<tr>
<td>5. Identify and minimize exposure to nephrotoxic agents</td>
<td>Nonsteroidal anti-inflammatory agents Aminoglycoside antibiotics Contrast dye</td>
</tr>
<tr>
<td>6. Provide timely referral to a nephrologist</td>
<td>Patients with evidence of renal impairment and/or proteinuria</td>
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</tbody>
</table>


47. Obrador GT, Pereira BJ. Early referral to the nephrologist and timely initiation of renal replacement therapy: a paradigm shift in the management of patients with chronic renal failure.


